practice fusion™
Free, web-based Electronic Health Records

Real World Evidence: Extended Release Opioids

A proposal for:

Pharma Co. X

Prepared by:

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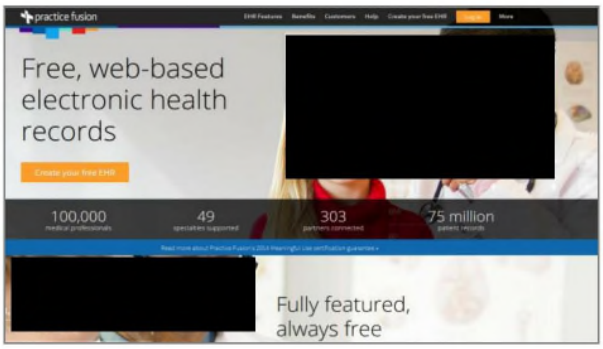
PRACTICE FUSION™ | The fastest growing healthcare platform

Practice Fusion's mission is to connect doctors, patients and data to drive better health and save lives. Founded in 2005, Practice Fusion pioneered an innovative, free, web-based model for electronic healthcare record (EHR) technology. Our real-time clinical platform powers the largest de- identified clinical dataset in the US.



From identifying disease outbreaks to tracking Meaningful Use progress, Practice Fusion's clinical research team is dedicated to helping medical practices deliver better, safer and more efficient care. Named a "Technology Pioneer" in 2013 and 2014 by the World Economic Forum, Practice Fusion is uniquely positioned to transform the health sector.

As the nation's largest and fastest-growing cloud based healthcare platform, Practice Fusion is a driving force in transforming US healthcare. Practice Fusion's real-time clinical EHR platform is also one of the largest clinical databases in the United States. One of Practice Fusion's main differentiators is our ability to intervene and message with both providers and their patients - before, during and after the patient visit enabling Practice Fusion to help implement and measure outcomes for multiple patient care interventions and programs.

Overview

The Practice Fusion Clinical Data Science team is pleased to present this real world evidence (RWE) proposal to investigate chronic pain among patients with a new prescription for an extended release opioid (ERO) to the HEOR Team at Pharma Co. X. The proposed project will be based on Electronic Health Record (EHR) data obtained through the Practice Fusion healthcare platform. Pharma Co. X is seeking to learn more about intensity of chronic pain as measured by pain score and ERO use in real world settings.

Data in the Practice Fusion EHR database is updated daily and allows for the timely review of current prescribing and treatment practices in the United States. The Practice Fusion operational strategy and final project plan will be developed once the project content and study design have been agreed upon with Pharma Co. X. Practice Fusion's response presents an analytic solution leveraging Practice Fusion's existing analytics platform and de-identified clinical patient level data collected via the Practice Fusion EHR Platform. The Practice Fusion EHR data covers all of these areas and will allow Practice Fusion to collaborate with Pharma Co. X on this retrospective analysis using real world data. With a rich clinical dataset, robust prescription fill data, and integrated labs with structured results all updated in real time – as well as a strong in-house

analytics team comprised of specialists in epidemiology, bio-informatics, and data science – Practice Fusion is an ideal partner for this project.

Objectives

The main goal of this study is to describe and evaluate provider and patient characteristics around newly written prescriptions for extended-release opioids. Focus will be on intensity of pain as measured by pain score among patients with chronic pain. This will be accomplished by reviewing and describing patient and provider data in the 6-month period leading up to new ERO prescription orders. Practice Fusion will evaluate the following objectives among patients receiving treatment with EROs for chronic pain:

Cross-Sectional Description of Treatment Landscape

1. Describe baseline patient and provider characteristics
2. Describe current pain scores by treatment (type, duration, strength)

Longitudinal Description of Pain Scores

1. Describe treatment patterns for chronic pain therapy
    - Describe and evaluate initiation of long-acting agents
2. Describe and evaluate change in pain scores over time
    - 50% reduction in pain score

The Practice Fusion database has the required patients and elements to address the proposed objectives. The focus of this project proposal is the Practice Fusion operational strategy, analytic methodology, and proposed deliverables.

Study Description

Practice Fusion proposes to conduct a retrospective database review on recent EHR data of chronic pain patients initiating an ERO (final definition to be determined based on discussion with Pharma Co. X). The evaluation will consist of both a cross-sectional component to describe current treatment patterns and a longitudinal patient-level description of change over time in pain management as measured by pain scores. The study period of interest will be from January 1, 2012 through most recent data available in order to focus on the contemporary landscape of opioid therapy and uptake of newer products. Diagnosis, pharmacy, vital signs and pain score data is required to provide a full picture of the total management of chronic pain patients.

Data Source

Data for the proposed project will be drawn from the Practice Fusion EHR database. The Practice Fusion EHR database consists of data collected through the Practice Fusion cloud-based ambulatory EHR platform. The Practice Fusion ambulatory EHR platform is currently in use at over 13,000 practices in all 50 US states. A majority of Practice Fusion practices are single provider or small group practices. Data is available for over 23Million unique patients starting in 2005, of which over 13 Million are currently active on the platform. Data is updated daily and is made available for analysis in a HIPAA-compliant de-identified research database on a weekly basis. A number of data validation and quality checks are performed as part of this process.

A comparison of the Practice Fusion ambulatory EHR database to information representative of the United States collected in the National Ambulatory Medical Care Survey (NAMCS) conducted by the Center for Disease Control (CDC), shows that Practice Fusion patients are similar in both demographic and clinical characteristics to utilizers of ambulatory healthcare in the United States (Appendix A).

The Practice Fusion EHR database includes information in the following domains:

- Patient demographics
  - Age, Gender, Race
  - Geographic region
- Patient characteristics
  - Weight, Height, BMI
  - Smoking status
- Provider characteristics
  - Physician specialty
  - Size of practice
- Office visits and chief complaints
- Diagnoses
- Prescriptions written and filled (with corresponding diagnosis)
- Tests and procedures
- Laboratory values
- Other measurements
- Ability to review provider notes

Methods

Data analysis will include two components:

1. Cross-Sectional Description of Treatment Landscape
2. Longitudinal Description of Pain Scores

Both components will be made up from patients with a new prescription written for one of the study medications of interest. The cross-sectional component will consist of a 'snapshot' of data from the 6 month period leading up to the index prescription order. The longitudinal

component will consist of a subset of these patients that have a minimum of 12 months of time in the database prior to the index prescription.

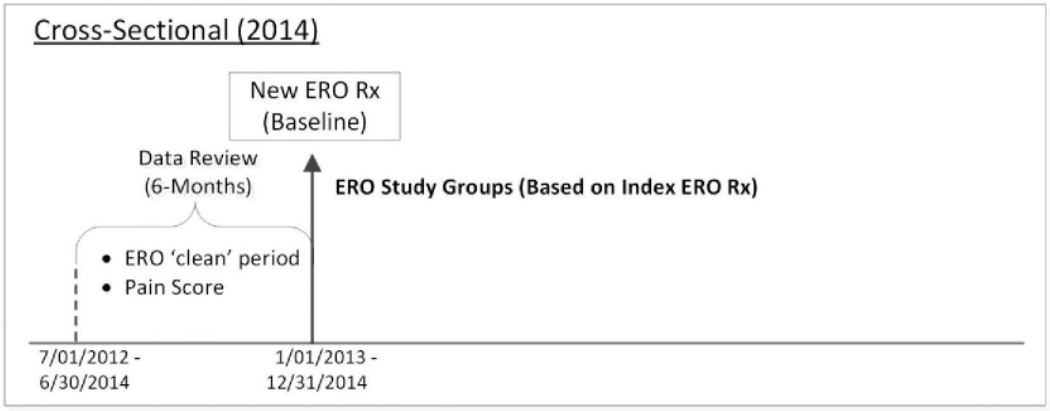
Cohort Selection & Follow-up

The study population will be selected from patients meeting the study inclusion criteria based on a combination of treatment types, diagnosis codes and pain score measures (final criteria to be determined based on discussion with Pharma Co. X. Data will be reviewed for the time period July 1, 2012 to December 31, 2014. Patients will be characterized by pain score and duration of treatment. Study groups will be defined based on treatment type. For the cross-sectional component data would be reviewed for the 6-month period prior to a recent new ERO prescription (Figure 1). For the longitudinal component an appropriate index date would be established (e.g., date of recent new ERO Rx) and patients would be followed for specified baseline pre-index and follow-up periods (e.g., 6-month baseline and 12 months follow-up) to explore project objectives (Figure 2). Study patients would be followed in the EHR database to evaluate project outcomes. Standard inclusion and exclusion criteria (e.g., current activity for the study duration, selected ages, treatments, and diagnoses) would be established with Pharma Co. X and implemented.

1. **Cross-Sectional Description of Treatment Landscape**

The cross-sectional component will be conducted first and will review new ERO prescription data for up to a two-year period of time.

FIGURE 1



Initial inclusion criteria:

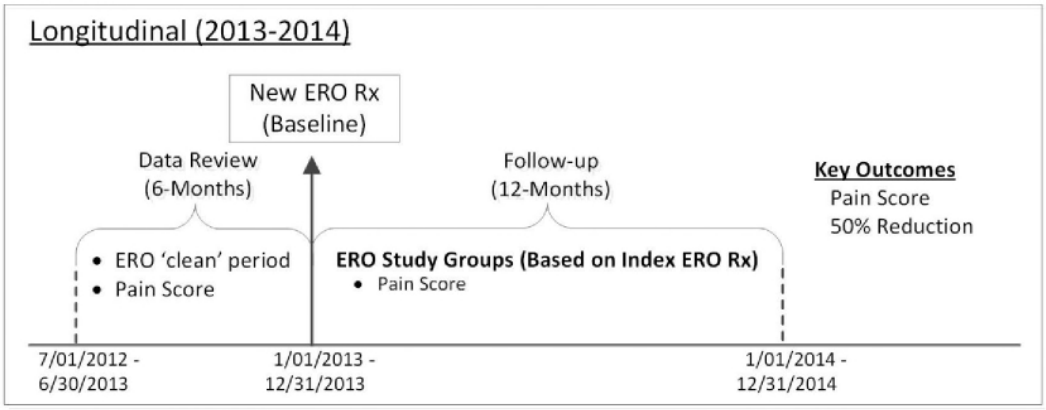
1. Age 18+
2. New prescription for Study ERO, (January 1, 2013 – December 31, 2014)
3. 6-months prior Index ERO, time in database
4. Diagnosis of chronic pain
    a. Chronic pain (ICD9: 338.2)
    b. Type of pain (e.g. back pain, lumbar pain, osteoarthritis)
    AND
    Duration of pain diagnosis greater than 3 months (chronic pain)

Descriptive tables based on review of data in the 6-month period prior to the Index ERO prescription will be developed. Tables will include provider specialty and prescribing volumes, patient demographics and clinical profiles including prior medication(s) and pain diagnoses.

2. **Longitudinal Description of Pain Scores**

Following the cross-sectional component a longitudinal review of data will be conducted for those patients that have sufficient time in the database to evaluate outcomes (change in pain score) after the cross-sectional review period.

FIGURE 2



Initial inclusion criteria:

1. Age 18+
2. New prescription for Study ERO, (January 1, 2013 – December 31, 2013)
3. 6-months prior and 12-months post Index ERO, time in database
4. Diagnosis of chronic pain
    a. Chronic pain (ICD9: 338.2)
    b. Type of pain (e.g. back pain, lumbar pain, osteoarthritis)
    AND
    Duration of pain diagnosis greater than 3 months (chronic pain)

Data Availability

Review of the Practice Fusion database for patients who have a new prescription written for an extended release (ER) opioid in the past 12 months shows approximately 10,000 patients are available for initial evaluation (Table 1). There are also sufficient counts of patients by product to allow for product specific reporting (Table 1). About 10 percent of patients have pain scores available in the period of interest, N= 835 (Table 2). This number will be sufficient to describe patients by level of pain but will not provide a large number of patients for analysis of change in pain score pre post ER opioid initiation.

TABLE 1 Patients with a New Rx for an Extended Release Opioid

Extended Release (ER) Opioids	Lookback time prior to Opioid Rx		
	>6m	>12m	>24m
Overall	**9,954**	**5,899**	**2,837**
Pharma Co. X	3,518	2,085	1,015
[redacted]	2,836	1,595	745
	1,774	1,149	610
	911	482	203
	764	465	235
	339	220	88
	259	172	79

TABLE 2 Patients with a New Rx for an Extended Release Opioid – with Pain Score

Extended Release (ER) Opioids	Lookback time prior to Opioid Rx		
	>6m	>12m	>24m
Overall	**835**	**554**	**320**
Pharma Co. X	344	232	131
[redacted]	281	173	105
	119	84	48
	79	54	32
	45	26	17
	26	20	14
	26	20	11

Data Elements & Specification of Study Measures

Descriptions will include top diagnoses in each group, providers in each group and details on treatment (e.g. dose, duration, strength) and treatment pattern (e.g. switching, combinations). Evaluation will focus on pain scores and other pain related information available in the electronic record. The study measures of interest are outlined below. These measures will be further developed and defined with Pharma Co. X during the development of the project analytic plan. A detailed list of measures and definitions including relevant diagnosis, procedure, and NDC codes would be submitted to Pharma Co. X for review and approval. To the extent feasible, standardized time frames, measures and units will be utilized. To evaluate and compare study groups, the following measures will be assessed for each study group:

1. Demographic characteristics
    a. Age

   b. Gender
   c. Geographic region
2. Provider characteristics
   a. Provider specialty
3. Opioid use & other pain therapy
   a. Type of treatment
   b. Date started treatment
   c. Length of time on treatment
   d. Strength of treatment
4. Chronic pain diagnosis (ICD9:)
   a. Diagnosis date
   b. Duration of diagnosis
5. Other pain diagnoses
   a. ICD9 code (selected types of pain)
   b. Diagnosis date
   c. Duration of diagnosis
6. Comorbidities
7. Pain scores
   a. Date
   b. Level (0-10)
8. Descriptors of pain
   a. Type of pain
   b. Location of pain
   c. Intensity of pain
   d. Other descriptors (from chart notes)

Existing extended release opioid (ERO) products on the market for consideration include:

- [redacted]
- Pharma Co. X
- [redacted]
- Pharma Co. X
- [redacted]
- [redacted]

Data Analysis

Data obtained from the EMR and claims files will be imported into and maintained in a project analytic data file on which all data analyses would be performed. Tabulation of summary

statistics, graphical presentations, and statistical analysis will be performed using statistical analysis tools (e.g., SAS). Demographics and baseline clinical characteristics of study patients including treatment will be described as counts and percentages for categorical variables and measures of central tendency (mean, median, standard deviation [SD], and min/max) for continuous variables (e.g., duration of therapy, pain score level). P values will be calculated for selected key variables only, using the Chi-square test for categorical variables, Wilcoxon rank sum test or t-test for continuous variables depending on the distribution of data. Ninety-five percent confidence intervals will be calculated for key parameters. Statistical tests will be two-sided, with a α-level of 0.05 for statistical significance unless otherwise stated.

Medication study groups would be compared according to provider and baseline patient demographic and clinical characteristics. Analyses stratified by diagnosis type, treatment pattern, and ERO type, duration, and strength would be conducted.

Tasks & Scope of Work

Proposed project tasks and deliverables in order that they would be completed:

Task One: Project Initiation and Communication Plan

At the outset of the project, members of the Pharma Co. X and Practice Fusion project teams will participate in an initial project kick-off meeting. The kick-off meeting will include discussion of project objectives and scope; project deliverables, timelines and milestones; and communication and meeting plan. During the course of the project, regular meetings will be held between the Pharma Co. X and Practice Fusion teams to review progress on the project and the project work plan. These meetings, which will be scheduled at project kick-off will ensure continued attention to project tasks and deliverables.

Assumptions

- Project initiation kick-off meeting will take place in a timely manner once contracted

Task Two: Analytic Plan

Following the kick-off meeting, Practice Fusion will prepare an Analytic Plan that describes the objectives of the project, the methodological approach, the project database, populations of interest, available sample sizes, outcomes to be evaluated, plans for data analysis, and table shells for presenting project findings. A draft of the analytic plan will be provided to Pharma Co. X for review and comment, after which it will be revised for final approval.

Assumptions

- The draft analytic plan will be delivered to Pharma Co. X within 6 weeks of project initiation.
- Pharma Co. X will review the draft document in a timely manner. Expected turn around for comments is 5-10 business days according to communication plan.

- Practice Fusion will finalize the analytic plan and provide to Pharma Co. X within 5-7 business days according to communication plan.

Task Three: Project Database

Practice Fusion will develop project-specific data files in support of the analytic plan. The project database or analytic data file will be created from source EHR data tables for patients meeting project inclusion criteria and maintained for the duration of the project.

Assumptions

- This task will be completed within 3-4 weeks of an approved analytic plan
- Data management will be subject to internal quality assurance procedures

Task Four: Preliminary Analyses and Results

Analyses will be conducted by Practice Fusion according to the analytic plan. Preliminary findings and specified format including table shells will be prepared and provided to Pharma Co. X for review and comment.

Assumptions

- Review and turn around according to project communication plan
- Meetings between the Pharma Co. X and Practice Fusion project teams will be held as needed
- Additional analyses beyond scope may result in added fees

Task Five: Final Analyses and Project Report

Comments from Pharma Co. X will be reviewed and final data analyses will be completed. The final set of result tables will be prepared and submitted to Pharma Co. X along with a Project Report.

Assumptions

- Review and turn around according to project communication plan
- Additional revisions beyond scope may result in added fees

TERMS | Project costs, terms, and payment schedule

The project will be initiated following formal written approval of this proposal by Pharma Co. X. The estimated timeframe and cost of data access and professional fees for this project are detailed below. This timeframe is based on an expected execution contract date of January 26, 2015.

The cost for the proposed project is $217,650 which includes professional fees associated with all aspects of conducting the proposed set of tasks, data management, and data access fee.

Project Tasks and Description	Timeline	Estimated Investment
TASK 1: Project Initiation & Communication • *Project Kick-Off; Communications; Meetings*	1/2015 - ongoing	$15,440
TASK 2: Analytic plan & Table shells • *Prepare project analytic plan* • *Draft output format, including table shells*	2/2015 - 3/2015	$40,200
TASK 3: Create Project Database • Cross-sectional set • Longitudinal set	3/2015	$29,510
TASK 4: Preliminary Analysis & Draft Results • *Review Preliminary Analyses with Client*	3/2015 - 4/2015	$33,200
TASK 5: Final Analysis & Project Report • *Finalize Analyses & Report*	4/2015 - 5/2015	$36,800
	Total Professional Fees	**$155,150**
	Data Access Fee	**$62,500**
	Total Investment	**$217,650**

Deliverables & Payment Schedule

The payment schedule outline below will be initiated following formal written approval of this proposal by Pharma Co. X. The estimated invoice date for each deliverable is based on task completion as above.

Deliverable Description	Invoice Timing	Invoice Amount
Contract Execution and Project Initiation + Data access fee	Week 2	$38,800
Delivery of Final Analytic Plan	Week 8	$65,200
Delivery of Preliminary Tables	Week 12	$56,825
Delivery of Final Project Report	Week 16	$56,825

APPENDIX A | Practice Fusion vs. NAMCS